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Prophylactic nimodipine treatment for cochlear and facial nerve preservation after vestibular schwannoma surgery: a randomized multicenter Phase III trial

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OBJECTIVE A pilot study of prophylactic nimodipine and hydroxyethyl starch treatment showed a beneficial effect on facial and cochlear nerve preservation following vestibular schwannoma (VS) surgery. A prospective Phase III trial was undertaken to confirm these results.

METHODS An open-label, 2-arm, randomized parallel group and multicenter Phase III trial with blinded expert review was performed and included 112 patients who underwent VS surgery between January 2010 and February 2013 at 7 departments of neurosurgery to investigate the efficacy and safety of the prophylaxis. The surgery was performed after the patients were randomly assigned to one of 2 groups using online randomization. The treatment group (n = 56) received parenteral nimodipine (1–2 mg/hr) and hydroxyethyl starch (hematocrit 30%–35%) from the day before surgery until the 7th postoperative day. The control group (n = 56) was not treated prophylactically.

RESULTS Intent-to-treat analysis showed no statistically significant effects of the treatment on either preservation of facial nerve function (35 [67.3%] of 52 [treatment group] compared with 34 [72.3%] of 47 [control group]) (p = 0.745) or hearing preservation (11 [23.4%] of 47 [treatment group] compared with 15 [31.2%] of 48 [control group]) (p = 0.530) 12 months after surgery. Since tumor sizes were significantly larger in the treatment group than in the control group, logistic regression analysis was required. The risk for deterioration of facial nerve function was adjusted nearly the same in both groups (OR 1.07 [95% CI 0.34–3.43], p = 0.91). In contrast, the risk for postoperative hearing loss was adjusted 2 times lower in the treatment group compared with the control group (OR 0.49 [95% CI 0.18–1.30], p = 0.15). Apart from dose-dependent hypotension (p < 0.001), no clinically relevant adverse reactions were observed.

CONCLUSIONS There were no statistically significant effects of the treatment. Despite the width of the confidence intervals, the odds ratios may suggest but do not prove a clinically relevant effect of the safe study medication on the preservation of cochlear nerve function after VS surgery. Further study is needed before prophylactic nimodipine can be recommended in VS surgery.

Clinical trial registration no.: 2009-012088-32 (www.clinicaltrialsregister.eu)

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KEY WORDS nimodipine; vestibular schwannoma; acoustic neuroma; neuroprotection; skull base

ABBREVIATIONS HES = hydroxyethyl starch; VS = vestibular schwannoma.

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Vestibular schwannomas (VSs) account for 6%–8% of all intracranial tumors. Management of patients with VS includes follow-up, radiotherapy, and microsurgery. However, the goal of modern VS surgery is total tumor removal with preservation of facial and cochlear nerve function.[17,18,19] With the exception of dexamethasone, there is a lack of neuroprotective medication in neurosurgical interventions. Nimodipine, a dihydropyridine calcium antagonist, is a generally well-tolerated drug with a long history in neurosurgical practice and is currently indicated in patients with aneurysmal subarachnoid hemorrhage.[3] The specific mechanism by which nimodipine may improve outcome has not been clearly defined, but besides preventing cerebral vasospasm a neuroprotective effect has been assumed.[16]

Therefore, nimodipine was administered to patients with loss or deterioration of intraoperative brainstem auditory evoked potential patterns in vestibular schwannoma surgery (off-label use).[2,24] Several authors following retro- and prospective clinical trials revealed a beneficial effect of nimodipine and hydroxyethyl starch (HES) on long-term outcome of cranial nerve function following VS surgery.[2,21,24,25] A pilot study showed a superiority of its prophylactic administration compared with an intraoperative start or no treatment.[20] The present Phase III trial was undertaken to examine whether prophylactic nimodipine and HES are beneficial in patients undergoing VS surgery.

Methods

Trial Design

A prospective, open-label, 2-arm, randomized, multicenter Phase III trial with blinded expert review was performed to investigate the efficacy and the safety of prophylactic parenteral nimodipine and HES treatment in VS surgery (clinical trial registration no. 2009-012088-32 [www.clinicaltrialsregister.eu]). A double-blind design was not feasible because parenteral administration of nimodipine required use of a central line for 7 days in the treatment group, and it was not considered ethical to impose this on control patients. This investigator-initiated trial was conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the German Competent Authority. The study protocol was positively reviewed by the Ethics Committee, University of Halle-Wittenberg, Germany, and all local review boards of the participating institutions. Each patient consented after being provided written information before being enrolled. No changes to methods were introduced after the trial was started.

Participants

The study enrolled patients 18 years of age or older with an indication for surgery of a VS. Exclusion criteria were contraindications against nimodipine or HES, preoperative facial nerve function (Grade VI according to the House-Brackmann grading scale),[7] surgery for recurrent VS, pregnancy and lactation period, neurofibromatosis Type 2, inoperability, and participation in other clinical trials within the last 30 days.

Interventions

Surgical procedures were performed by experienced surgeons at 7 German university hospitals. Gross-total resection of the VS via a retrosigmoid approach with preservation of facial and cochlear nerve function was the goal of all procedures. Intraoperative neurophysiological monitoring, including brainstem auditory evoked potentials and continuous facial nerve electromyography, and direct facial nerve stimulation were applied to all patients. Histopathological examinations were performed in all patients.

A total of 112 patients were randomly assigned to the treatment group (n = 56) or the control group (n = 56). Patients in the treatment group received a neuroprotective prophylaxis consisting of parenteral nimodipine (1–2 mg/hr; Nimotop, Bayer) and HES 6% (aimed at a hematocrit between 30% and 35%; Voluven 6%, Fresenius Kabi), which was started the day before surgery and was continued until the 7th postoperative day. In 2 patients in the treatment group, prophylaxis was not started until the day of surgery but before skin incision. A reduced duration of nimodipine therapy was observed in 11 patients, and a prolonged administration of nimodipine was documented in 2 patients. The administration of nimodipine was started preoperatively via a peripheral venous catheter with a dose of 1 mg/hr for 2 hours. Then, the dose was increased to 2 mg/hr. After induction of narcosis, nimodipine was given via a routinely placed central line. The full dose of 2 mg/hr was tolerated by 21 patients. Symptomatic hypotension with headaches or dizziness was observed in 26 patients resulting in a dose reduction to 1 mg/hr. In response, these dose-dependent symptoms were reversible. A strict lower blood pressure limit together with a dose reduction was not defined in asymptomatic patients. No patient experienced local pain in the area of the peripheral venous catheter following the start of nimodipine infusion. HES was administered preoperatively in 47 patients in the therapy group. In 35 patients HES was given according to schedule until the 7th postoperative day. A reduced duration of HES treatment was documented in 12 patients.

The patients in the control group were not treated prophylactically. However, when intraoperative monitoring indicated deterioration of facial or cochlear nerve function, an intraoperative start of the neuroprotective therapy in the control group was permitted because of its beneficial effect in previous studies.[2,20,21,24,25] Therefore, neuroprotective therapy was started intraoperatively in 17 patients in the control group.

Outcomes, Follow-Up, and Blinding

Function of the facial nerve 12 months after surgery compared with its function before surgery was assessed as the primary outcome. Secondary outcomes were cochlear nerve function 12 months after surgery and adverse events.

Facial function was documented photographically at rest and in motion as described by House and Brackmann at defined time points (preoperatively; immediately postoperatively; and 3, 6, and 12 months after surgery).[7] Photographs were evaluated by a blinded neurologist experienced in the assessment of facial nerve disturbances and classified using the House-Brackmann grading scale.

Hearing ability was determined by pure-tone audiometry with speech discrimination. Speech audiograms were performed preoperatively, in the early postoperative course, and 12 months after surgery, analyzed by a blinded otorhinolaryngologist, and classified using the Gardner-Robertson scale.[4]

Tumor size (according to the Koos grading system) and extent of resection were evaluated by a blinded neuroradiologist on the basis of axial contrast-enhanced T1-weighted MRI performed preoperatively and 3 months after surgery.[11]

Side effects, concomitant medication, and comorbidities were documented descriptively. Due to the possible blood pressure–lowering effect of nimodipine, blood pressure was carefully monitored.

There were no changes in the trial protocol after the trial started.

Sample Size

Sample size was determined based on the assumption of 50% worsening of the facial nerve function in the control group and of 15% worsening in the treatment group.[20] A 2-sided chi-square test with continuity correction and significance level of 5% and a power of 95% was performed. This would require 50 patients per group. Because it was expected that 10% of patients would drop out, the final sample size was fixed with 56 patients per group. No interim analysis was planned or performed.

Randomization

Participants were enrolled and assigned to intervention by the investigator of each trial site using an online randomization tool provided by the Coordination Centre for Clinical Trials (KKS), University of Halle-Wittenberg, Germany. The software used to generate the random allocation sequence was SAS (version 9.1, SAS Institute), procedure "plan" with block randomization, created at KKS Halle. Blocking was done by the trial center.

Statistical Methods

Preservation of the facial and cochlear nerve function 1 year after surgery in comparison with the preoperative findings was analyzed using logistic regression to allow adjustment with respect to tumor size and extent of resection. Tumor size shows a relative imbalance in the distribution over treatment group and control group despite a proper randomization procedure, with larger tumors in the treatment group (Table 1). Odds ratios and their 95% confidence intervals were calculated.

Binary outcomes were compared using Fisher's exact test. For the evaluation of hearing functions at different postoperative time points, the chi-square-test was used. Additional analysis was performed in subgroups with large tumor size.

Results

Participant Flow

A total of 146 patients were screened; 34 patients did not meet inclusion criteria, declined to participate, or had other reasons for exclusion. Therefore, 112 patients were enrolled and randomly assigned to the treatment group (n = 56) or the control group (n = 56). Nine patients in the treatment group and 8 patients in the control group had to be excluded from analysis because of the reasons shown in Fig. 1.

Accordingly, 47 (84%) patients in the treatment group and 48 (86%) patients in the control group were suitable for statistical analysis.

TABLE 1. Baseline data*

Variable	Treatment Group (n = 47)	Control Group (n = 48)
Mean age in yrs ± SD	48.4 ± 13.0	48.8 ± 12.5
Sex		
Female	26 (55.3)	28 (58.3)
Male	21 (44.7)	20 (41.7)
Koos grade (tumor size)		
I	0	1 (2.1)
II	13 (27.7)	22 (45.8)
III	23 (48.9)	16 (33.3)
IV	11 (23.4)	9 (18.8)
GR class (preop hearing)		
I	18 (38.3)	15 (31.2)
II	15 (31.9)	14 (29.2)
III	14 (29.8)	16 (33.3)
IV	0	0
V	0	3 (6.2)
HB grade (preop facial nerve function)		
I	45 (95.7)	47 (97.9)
II	2 (4.3)	1 (2.1)

GR = Gardner-Robertson; HB = House-Brackmann.
* Data are presented as no. (%) unless otherwise indicated.

Recruitment

The entire course of the study lasted from January 27, 2010, to February 26, 2013. Recruitment was planned from January 2010 (first patient in) to December 2011. Complete enrollment of all 112 patients was achieved ahead of schedule in April 2011 (last patient in). Follow-up examinations at least 1 year after surgery were finished in February 2013 (last patient out).

Baseline Data

Both the therapy group and the control group were comparable in terms of age, sex, and preoperative cranial nerve function, but not in terms of tumor size (Table 1). In the treatment group more moderately large, large-, and giant-sized (Koos Grades III and IV, 72.3%) than small- and medium-sized tumors (Koos Grade II, 27.7%; no Koos Grade I tumors) were observed.[10] In contrast, the relation of tumor sizes in the control group was 47.9% of Koos Grade I and II and 52.1% of Koos Grade III and IV tumors.

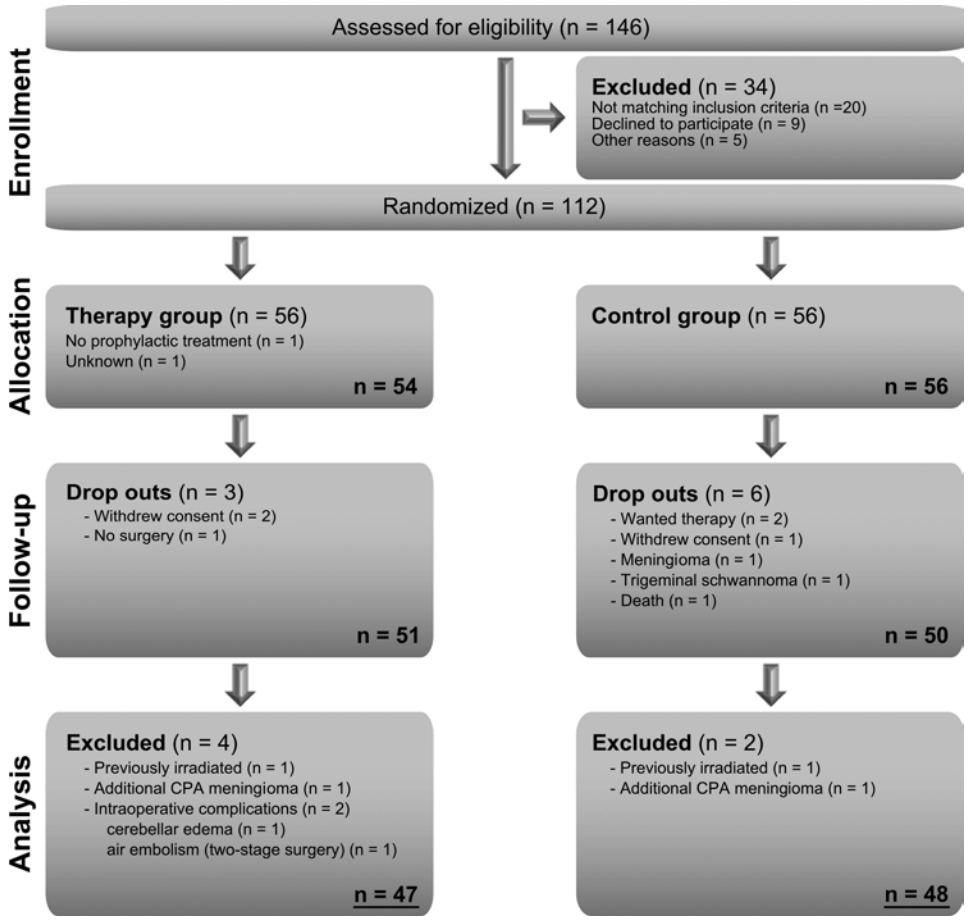

FIG. 1. Participant flow diagram. CPA = cerebellopontine angle.

Extent of resection was comparable with complete removal in 40 patients in both groups, capsule remnants (1–3 mm) in 4 patients in the treatment group and in 3 patients in the control group, and subtotal removal (3–10 mm) in 3 patients in the therapy group and in 5 patients in the control group, based on the evaluation of axial T1-weighted and contrast-enhanced MR images by a blinded neuroradiologist.

Intraoperative Findings and Number Analyses

Facial Nerve

The anatomical continuity of the facial nerve was lost during tumor dissection in 2 patients in the treatment group. Both patients were excluded from further analysis concerning preservation of facial nerve function but were still included in the assessment of cochlear nerve function.

Cochlear Nerve

Preservation of the cochlear nerve was achieved in 30 (63.8%) patients in the treatment group and in 35 (72.9%) patients in the control group. In 4 patients in the treatment group, the internal auditory artery was occluded during tumor resection, resulting in abrupt loss of brainstem auditory evoked potentials and postoperative ipsilateral hearing loss. Therefore, these patients were excluded from further analysis of hearing preservation but were still considered in the analysis of facial nerve function.

Outcomes and Estimation

Facial Nerve Function 1 Year After Surgery

The rate of preservation of facial nerve function of House-Brackmann Grades I–III was 45 of 45 (100%) for each tumor size (Koos Grades II–IV) in the treatment group. In the control group House-Brackmann Grades I–III were observed in 39 of 39 patients (100%) of Koos Grade I, II, and III tumors, and in 7 of 9 (78%) of Koos Grade IV tumors. Analyzing the chance of postoperative excellent facial nerve function (House-Brackmann Grades I and II), there was no major difference in the overall preservation rate, with 38 of 45 (84%) in the treatment group versus 40 of 48 (83%) in the control group. For Koos Grade IV tumors, the treatment group showed higher preservation rates of House-Brackmann Grades I and II (6 of 9 [67%] vs 5 of 9 [56%] in the control group). Exclusively, 2 patients in the control group harboring Koos Grade IV tumors retained a severe facial nerve paresis (House-Brackmann Grades IV and V) 1 year after surgery (Table 2).

Hearing Preservation 1 Year After Surgery

Despite the fact that tumor sizes were larger in the treat-

TABLE 2. Facial and cochlear nerve function 1 year after surgery in relation to tumor sizes and in total

Group	Koos Grade				
	I	II	III	IV	Total
Treatment (n = 47)					
HB scale score					
I & II	0	92% (12/13)	87% (20/23)	55% (6/11)	81% (38/47)
I–III	0	92% (12/13)	100% (23/23)	82% (9/11)	94% (44/47)
GR class					
I–IV	0	62% (8/13)	38% (8/23)	18% (2/11)	38% (18/47)
I–III	0	62% (8/13)	38% (8/23)	18% (2/11)	38% (18/47)
I & II	0	31% (4/13)	29% (5/23)	0 (0/11)	19% (9/47)
Control (n = 48)					
HB scale score					
I & II	100% (1/1)	91% (20/22)	88% (14/16)	56% (5/9)	83% (40/48)
I–III	100% (1/1)	100% (22/22)	100% (16/16)	78% (7/9)	96% (46/48)
GR class					
I–IV	100% (1/1)	45% (10/22)	25% (4/16)	0 (0/9)	31% (15/48)
I–III	100% (1/1)	41% (9/22)	25% (4/16)	0 (0/9)	29% (14/48)
I & II	100% (1/1)	18% (4/22)	25% (4/16)	0 (0/9)	19% (9/48)

ment group than in the control group, hearing preservation (Gardner-Robertson Classes I–IV) was achieved in 18 of 43 (42%) of all patients in the treatment group, compared with 15 of 48 (31%) in the control group. However, Fisher's exact test was not significant ($p = 0.38$). Analyzing hearing preservation of Gardner-Robertson Classes I–III showed similar results with 18 of 43 (42%) of the treatment group versus 14 of 48 (29%) in the control group ($p = 0.27$). Postoperative excellent hearing (Gardner-Robertson Classes I and II) was observed in 10 of 43 (23%) in the treatment group and in 9 of 48 (19%) of the control group ($p = 0.62$). Hearing preservation (Gardner-Robertson Classes I–IV and I–III) in Koos Grade IV tumors was achieved in 2 of 10 (20%) in the treatment group, whereas all patients (9 of 9) in the control group became deaf ($p = 0.47$). Postoperative excellent hearing preservation (Gardner-Robertson Classes I and II) was not achieved in Koos Grade IV tumors in either group. As shown in Table 2, there was a tendency for a better outcome for hearing in the treatment group than in the control group in all subclasses (Gardner-Robertson class and Koos grade). There were no differences between hearing abilities in the early postoperative course and 1 year after surgery ($p < 0.001$), reflecting the missing regeneration potential of the cochlear nerve in VS surgery.

Intent-to-treat analysis showed no statistically significant effects of the treatment on both preservation of facial nerve function (35 [67.3%] of 52 [treatment group] vs 34 [72.3%] of 47 [control group]) ($p = 0.745$) and hearing preservation (11 [23.4%] of 47 [treatment group] vs 15 [31.3%] of 48 [control group]) ($p = 0.530$) 12 months after surgery. However, tumors were significantly larger in the treatment group than in the control group. Tumor size is the most important predictor for the preservation of facial and cochlear nerve function after VS surgery.[17] Due to the unexpected unequal distribution of tumor sizes between groups and the slight differences concerning the extent of resection, additional statistical analysis was adjusted for tumor size and extent of resection in both groups using logistic regression. This additional analysis was not prespecified in the protocol and statistical analysis plan.

The risk for deterioration of facial nerve function was adjusted nearly the same in both groups (OR 1.07 [95% CI 0.34–3.43], $p = 0.91$). In contrast, the risk for deterioration of cochlear nerve function to postoperative Gardner-Robertson Class V (OR 0.49 [95% CI 0.18–1.30], $p = 0.15$) or to Gardner-Robertson Class IV or V (OR 0.45 [95% CI 0.17–1.20], $p = 0.11$) was adjusted 2 times lower in the treatment group compared with the control group (Table 3). Subgroup analysis of patients with preoperative Gardner-Robertson Classes I–IV and tumor sizes of Koos Grades III and IV showed a 3 times lower risk for postoperative Gardner-Robertson Class V in the treatment group (OR 0.30 [95% CI 0.05–2.72], $p = 0.32$).

Adverse Effects of Treatment

In no instance was the study discontinued due to adverse events caused by the study medication. No death or serious adverse events caused by the study medication occurred in the treatment group, whereas 1 patient in the control group died of unknown reasons several weeks after surgery. Study medication was applied to this patient due to deterioration of cranial nerve function from the 1st until the 6th postoperative day. With nimodipine, the most common adverse event was dose-dependent hypotension ($p < 0.001$, chi-square test). Hypotension was observed in 26 of 47 (55%) patients in the treatment group and only in 6 of 48 (12%) patients in the control group. No other adverse events significantly differed between the groups (Table 4).

TABLE 3. Logistic regression adjusted for tumor size for facial and cochlear nerve function 1 year after surgery: risks for deterioration of cochlear and facial nerve function

Parameter	OR (treatment/control group)	95% CI
Deterioration of cochlear nerve function to postop GR class		
All tumor sizes		
GR Class V	0.49	0.18–1.30 (p = 0.15)
Preop GR Class V excluded	0.54	0.20–1.43 (p = 0.21)
GR Classes IV & V	0.45	0.17–1.20 (p = 0.11)
Subanalysis for Koos Grades III & IV		
GR Class V	0.47	0.12–1.80 (p = 0.27)
Preop GR Class V excluded	0.30	0.05–2.72 (p = 0.32)
GR Classes IV & V	0.47	0.12–1.80 (p = 0.27)
Deterioration of facial nerve function to postop HB grade		
All tumor sizes		
HB Grades III–V	1.07	0.34–3.43 (p = 0.91)
Subanalysis for Koos Grades III & IV		
HB Grades III–V	1.11	0.30–4.19 (p = 0.88)

Discussion

Limitations

This is the first prospective, randomized, multicenter Phase III trial investigating the influence of a neuroprotective prophylaxis in VS surgery. Several factors are known to have impact on the outcome of both the facial and the cochlear nerves after VS surgery. This and the number of patients might be the explanation for the large width of the 95% confidence intervals in Table 3. Despite the width of the confidence intervals (all including 1), the observed odds ratios for the risk of deterioration of cochlear nerve function in the treatment group as compared with the control group point to a beneficial effect of the safe study medication. Certainly, the main criteria for preservation of cranial nerve function in VS surgery are tumor size and experience of the surgeon.[17] Under these circumstances the efficacy of an additionally applied medication is not easy to quantify. The power of the study is decreased by the unexpected significantly different tumor sizes in the control group compared with the treatment group, requiring logistic regression analysis, and by the potential bias of a non–double-blind design. Furthermore, optimal dosages and the optimal duration of prophylactic nimodipine treatment should be investigated in the future.

Facial Nerve

The main differences between both groups were noted in large tumors (Koos Grade IV) with a preservation rate for House-Brackmann Grades I–III of 100% in the treatment group as compared with 78% in the control group and for House-Brackmann Grades I and II of 67% in the treatment group and 56% in the control group. These excellent functional outcomes in both groups are in accordance with the results of other experienced surgeons.[17–19] However, logistic regression analysis revealed no differences between the groups (Table 3).

Cochlear Nerve

Hearing preservation rates (Gardner-Robertson Classes I–IV) were 42% in the treatment group and 31% in the control group. These outcomes are also comparable with the results (46%–51%) of other experienced surgeons.[17] All patients with Koos Grade IV tumors in the control group lost hearing in the operated ear after surgery, whereas in 20% of the patients with Koos Grade IV tumors in the treatment group a postoperative hearing ability of Gardner-Robertson Class III was observed. Logistic regression showed that the risk for deterioration of cochlear nerve function to postoperative Gardner-Robertson Class V (OR 0.49 [95% CI 0.18–1.30], p = 0.15) or to Gardner-Robertson Class IV or V (OR 0.45 [95% CI 0.17–1.20], p = 0.11) was adjusted 2 times lower in the treatment group compared with the control group (Table 3). Subgroup analysis of patients with preoperative Gardner-Robertson Classes I–IV and tumor sizes of Koos Grades III and IV revealed a 3 times lower risk for postoperative Gardner-Robertson Class V in the treatment group (OR 0.30 [95% CI 0.05–2.72], p = 0.32).

Consequently, for the cochlear nerve preservation, the neuroprotective efficacy of the study medication was more apparent (decreasing odds ratio) with ascending tumor sizes (Koos Grade III and IV tumors).

Study Medication

As previously published, HES was administered for mild hemodilution.[2,20,24,25] The last patient was included before the "Public Workshop: Risks and Benefits of Hydroxyethyl Starch Solutions" of the FDA had taken place. Although Voluven 6% is approved by the FDA and no adverse events related to HES (especially renal toxicity) were observed in the present study, the neuroprotective effect of HES is questionable, taking into consideration that animal experiments and clinical trials using nimodipine alone showed evidence of comparable neuroprotective efficacy.[1,6,8,9,12–15,23]

From a pharmacokinetic point of view, parenteral ni-

TABLE 4. Adverse events

Adverse Events	Treatment Group (n = 47)	Control Group (n = 48)
Nausea*	28	28
Headache*	21	15
Hypotension*	26	6
Pain	10	14
Insomnia	7	6
Dizziness*	7	4
Urinary tract infection	0	3
Hypokalemia	3	0
Nystagmus	2	1
Acidosis	2	0
Tenseness	1	1
Hyperglycemia	1	1
Depression	1	1
Eye inflammation	1	1
Hypertension	0	1
Fever	1	0
Mood swing	1	0
Hyponatremia	0	1
Thrombophlebitis	1	0
Potassium deficiency	0	1
Late facial nerve paresis	0	1
ALT increase*	1	0
GGT increase*	1	0
Tachycardia*	1	0
Allergic reaction*	1	0
Serious adverse events		
CSF fistula	2	3
Thrombosis	0	1
Intraoperative air embolism	1	1
Bilateral pulmonary embolism	1	0
Intraoperative cerebellar swelling	1	0
Occlusive hydrocephalus	1	0
Subdural hematoma	1	0
Cerebellar infarction	1	0

ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase.
* Potentially caused by nimodipine.

modipine produces higher drug levels and has a higher neuroprotective efficacy compared with enteral administration.[22] Therefore, a central venous access is needed. The optimal duration of postoperative treatment should be investigated in further studies.

Generalizability

The beneficial effect of nimodipine treatment for the protection and regeneration of the facial and cochlear nerves is supported by animal experiments[1,6,8,9,12–15] and clinical trials in VS surgery.[2,20,21,24,25] Furthermore, these positive results were also observed in laryngeal[8,14] and maxillofacial surgery[23] and may therefore be transferable to other surgical procedures with nerves at risk.

Conclusions

There were no statistically significant effects of the treatment. Despite the width of the confidence intervals, the odds ratios may suggest but do not prove a clinically relevant effect of the safe study medication on the preservation of cochlear nerve function after vestibular schwannoma surgery. From the clinical and laboratory investigations, it has been observed that nimodipine probably exerts a positive effect on the preservation of both the facial and the cochlear nerve function after VS surgery. Besides dose-dependent hypotension and its possibly intraoperative negative impact on postoperative auditory function,[5] nimodipine is a safe drug. Nimodipine's efficacy is apparently higher with regard to preservation of cochlear nerve function, especially in large tumors. A prospective, randomized Phase III study of prophylactic nimodipine treatment in 200 patients with preoperative hearing classes of Gardner-Robertson Class I–III suffering from Koos Grade III and IV tumors should be consecutively performed.

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Registration and Protocol

The study was registered before starting enrollment with the EudraCT number 2009-012088-32; KKSH-66; DRKS 00000328 and with the name "AkNiPro."

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